09/ 910,702

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

09/ 910,702

FILE 'HOME' ENTERED AT 16:52:51 ON 19 SEP 2002

=> file reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 16:53:00 ON 19 SEP 2002

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 18 SEP 2002 HIGHEST RN 452896-77-4
DICTIONARY FILE UPDATES: 18 SEP 2002 HIGHEST RN 452896-77-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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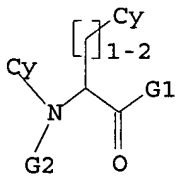
Uploading 09910702.str

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 O,N

G2 H,Cy,Ak

Structure attributes must be viewed using STN Express query preparation.

=> s (pyrimidin? or thiadiazol? or pyridazin? or pyrazin?)
636120 PYRIMIDIN?
122107 THIADIAZOL?
103648 PYRIDAZIN?
88606 PYRAZIN?
L2 937382 (PYRIMIDIN? OR THIADIAZOL? OR PYRIDAZIN? OR PYRAZIN?)

=> s l1
SAMPLE SEARCH INITIATED 16:53:43 FILE 'REGISTRY'

09/ 910,702

SAMPLE SCREEN SEARCH COMPLETED - 72593 TO ITERATE

1.4% PROCESSED 1000 ITERATIONS 3 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
BATCH **INCOMPLETE**
PROJECTED ITERATIONS: EXCEEDS 1000000
PROJECTED ANSWERS: EXCEEDS 3470

L3 3 SEA SSS SAM L1

=> s l1 ful
FULL SEARCH INITIATED 16:53:50 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - >1,000,000 TO ITERATE

< 10.7% PROCESSED 107088 ITERATIONS 774 ANSWERS
<------User Break------>
u
< 14.9% PROCESSED 148952 ITERATIONS 838 ANSWERS
SEARCH ENDED BY USER
SEARCH TIME: 00.00.20

FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
BATCH **INCOMPLETE**
PROJECTED ITERATIONS: EXCEEDS 1000000
PROJECTED ANSWERS: EXCEEDS 7873

L4 838 SEA SSS FUL L1

=> s l1 sub=l2
ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):full
FULL SUBSET SEARCH INITIATED 16:54:29 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED - 38339 TO ITERATE

100.0% PROCESSED 38339 ITERATIONS 619 ANSWERS
SEARCH TIME: 00.00.03

L5 619 SEA SUB=L2 SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	296.94	297.15

FILE 'CAPLUS' ENTERED AT 16:54:39 ON 19 SEP 2002

FILE COVERS 1907 - 19 Sep 2002 VOL 137 ISS 12

09/ 910,702

FILE LAST UPDATED: 18 Sep 2002 (20020918/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l5
L6 500 L5

=> s l6 and leukocyte?
78213 LEUKOCYTE?
L7 14 L6 AND LEUKOCYTE?

=> d l7 1- ibib abs fhitstr
YOU HAVE REQUESTED DATA FROM 14 ANSWERS - CONTINUE? Y/(N):y

L7 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:521509 CAPLUS
DOCUMENT NUMBER: 137:88482
TITLE: Combined use of enzyme inhibitors and pharmaceutical preparations thereof for the treatment and prophylaxis of arteriosclerosis, type I allergic reactions, and dermatological diseases associated with follicular and epidermal hyperkeratosis
INVENTOR(S): Ansorge, Siegfried; Lendeckel, Uwe; Neubert, Klaus; Reinhold, Dirk; Vetter, Robert; Gollnick, Harald
PATENT ASSIGNEE(S): Institut Fuer Medizintechnologie Magdeburg G.m.b.H., Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053170	A2	20020711	WO 2001-EP15199	20011221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10100052	A1	20020711	DE 2001-10100052	20010102
DE 10102392	A1	20020814	DE 2001-10102392	20010119

PRIORITY APPLN. INFO.: DE 2001-10100052 A 20010102
DE 2001-10102392 A 20010119
DE 2001-10155093 A 20011109
OTHER SOURCE(S): MARPAT 137:88482
AB The invention discloses the use of inhibitors of dipeptidyl peptidase IV (DPP IV) and enzymes having the same substrate specificity, combined with inhibitors of alanyl aminopeptidase (aminopeptidase N), or enzymes having the same substrate specificity, for the additive to superadditive inhibition of the activation and proliferation (DNA synthesis) of human T lymphocytes or mononuclear cells and of the prodn. of TH2 cytokines for

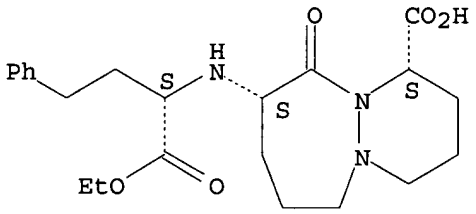
the treatment and prevention of allergic reactions of type I (according to the Gell and Coombs classification), for the additive to superadditive inhibition of the activation and proliferation (DNA synthesis) of human epidermal and follicular keratinocytes and those of the transition region between the skin and the mucosa, and for the treatment and prevention of dermatol. diseases assocd. with follicular and epidermal hyperkeratosis and increased keratinocyte proliferation. The invention also discloses the use of DPP IV and enzymes having the same substrate specificity, combined with inhibitors of aminopeptidase N or enzymes having the same substrate specificity, inhibitors of X-pro-aminopeptidase (aminopeptidase P), inhibitors of angiotensin-converting enzyme (ACE) and/or of prolyloligopeptidase (prolylendopeptidase) for the additive to superadditive inhibition of the activation, DNA synthesis and proliferation of human T lymphocytes or mononuclear cells for the treatment and prophylaxis of arteriosclerosis. The invention further discloses pharmaceutical prepns. comprising a plurality of inhibitors of the above enzymes.

IT **88768-40-5**, Cilazapril
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme inhibitor combinations for treatment of arteriosclerosis, type I allergic reactions, and dermatol. diseases assocd. with follicular and epidermal hyperkeratosis)

RN 88768-40-5 CAPLUS

CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:90040 CAPLUS

DOCUMENT NUMBER: 136:135022

TITLE: Preparation of heteroaryl-.beta.-alanine derivatives as antiinflammatory agents and .alpha.4 integrin inhibitors

INVENTOR(S): Konradi, Andrei W.; Pleiss, Michael A.; Thorsett, Eugene D.; Ashwell, Susan; Welmaker, Gregory S.; Kreft, Anthony; Sarantakis, Dimitrios; Dressen, Darren B.; Grant, Francine S.; Semko, Christopher; Xu, Ying-Zi

PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; American Home Products Corporation

SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

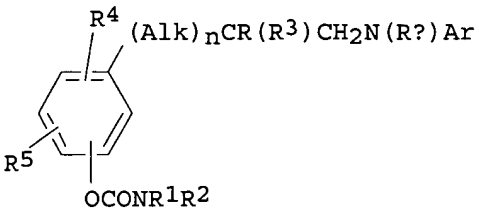
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2002008222 A2 20020131 WO 2001-US23096 20010720
WO 2002008222 A3 20020613
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2002086882 A1 20020704 US 2001-910431 20010719
PRIORITY APPLN. INFO.: US 2000-220128P P 20000721
OTHER SOURCE(S): MARPAT 136:135022
GI



I

AB Disclosed are a series of heteroaryl-.beta.-alanine derivs. I wherein R is a carboxylic acid; R1 and R2 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, or R1 and R2, together with the nitrogen atom to which they are attached, are joined to form an optionally substituted heterocyclic ring provided that said substituted alkyl, substituted alkenyl and substituted cycloalkyl do not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group; Ra and R3 are independently a hydrogen or a Me group; R4 and R5 are independently selected from the group consisting of heteroatom group; n is zero or an integer 1; Alk is a straight or branched alkylene chain; Ar is an optionally substituted arom. or heteroarom. group, as well as their pharmaceutical use as .alpha.4.beta.7 Integrin inhibitors for the treatment of inflammatory diseases. Thus, 3-[4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl]-2-(3-chlorophenylamino)propanoic acid was prepd. as .alpha.4 Integrin inhibitor. The preferred compds. of the invention generally have IC50 values in the .alpha.4.beta.1 and .alpha.a.beta.7 assays of 1 .mu.M and below. In the other assays featuring .alpha. integrins of other subgroups the same compds. had IC50 values of 50 .mu.M and above thus demonstrating the potency and selectivity of their action against .alpha.4 integrins. Title compds. were prepd. for treating an inflammatory condition in a mammalian patient which condition is mediated by Very Late Antigen 4 (VLA-4). Inflammatory condition is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute **leukocyte**-mediated lung injury.

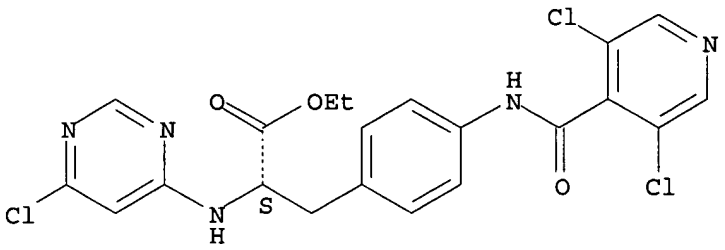
IT **263274-39-1P**
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES

(Uses)
(prepn. of heteroaryl-.beta.-alanine derivs. as antiinflammatory agents and .alpha.4 integrin inhibitors)

RN 263274-39-1 CAPLUS

CN L-Phenylalanine, N-(6-chloro-4-pyrimidinyl)-4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:90026 CAPLUS

DOCUMENT NUMBER: 136:135019

TITLE: Preparation of 3-amino-2-(4-aminocarbonyloxy)phenyl-propionic acid derivatives as antiinflammatory agents and .alpha.4 Integrin inhibitors

INVENTOR(S): Konradi, Andrei W.; Pleiss, Michael A.; Thorsett, Eugene D.; Ashwell, Susan; Welmaker, Gregory S.; Kreft, Anthony; Sarantakis, Dimitrios; Dressen, Darren B.; Grant, Francine S.; Xu, Ying-Zi

PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; American Home Products Corporation

SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

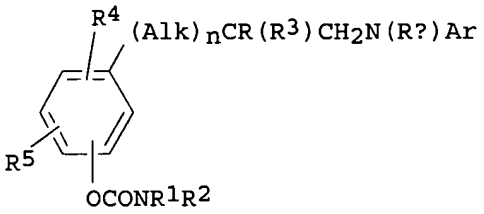
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008206	A1	20020131	WO 2001-US23073	20010720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002055509	A1	20020509	US 2001-910685	20010720

PRIORITY APPLN. INFO.: US 2000-220134P P 20000721

OTHER SOURCE(S): MARPAT 136:135019

GI



I

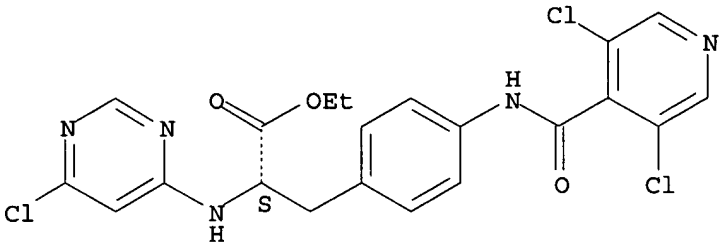
AB 3-Amino-2-(4-aminocarbonyloxy)phenyl-propionic acid derivs. I wherein R is a carboxylic acid; R1 and R2 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, or R1 and R2, together with the nitrogen atom to which they are attached, are joined to form an optionally substituted heterocyclic ring provided that said substituted alkyl, substituted alkenyl and substituted cycloalkyl do not carry an aryl, substituted aryl, heteroaryl or substituted heteroaryl group; Ra and R3 are independently a hydrogen or a Me group; R4 and R5 are independently selected from the group consisting of heteroatom group; n is zero or an integer 1; Alk is a straight or branched alkylene chain; Ar is an optionally substituted arom. or heteroarom. group, as well as their pharmaceutical use as .alpha.4.beta.7 Integrin inhibitors for the treatment of inflammatory diseases. Thus, 3-[4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl]-2-(3-chlorophenylamino)propanoic acid was prepd. as .alpha.4 Integrin inhibitor. The preferred compds. of the invention generally have IC50 values in the .alpha.4.beta.1 and .alpha.a.beta.7 assays of 1 .mu.M and below. In the other assays featuring .alpha. integrins of other subgroups the same compds. had IC50 values of 50 .mu.M and above thus demonstrating the potency and selectivity of their action against .alpha.4 integrins. Title compds. were prepd. for treating an inflammatory condition in a mammalian patient which condition is mediated by Very Late Antigen 4 (VLA-4). Inflammatory condition is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute **leukocyte**-mediated lung injury.

IT **263274-39-1P**
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of aminoaminocarbonyloxyphenylpropionic acid derivs. as a integrin inhibitors)

RN 263274-39-1 CAPLUS

CN L-Phenylalanine, N-(6-chloro-4-pyrimidinyl)-4-[[(3,5-dichloro-4-pyridinyl)carbonyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:90023 CAPLUS
DOCUMENT NUMBER: 136:135018
TITLE: Preparation of 3-(heteroaryl) alanine derivatives as inhibitors of **leukocyte** adhesion mediated by VLA-4
INVENTOR(S): Konradi, Andrei W.; Pleiss, Michael A.; Thorsett, Eugene D.; Ashwell, Susan; Welmaker, Gregory S.; Kreft, Anthony; Sarantakis, Dimitrios; Dressen, Darren B.; Grant, Francine S.; Semko, Christopher; Xu, Ying-Zi; Stappenbeck, Frank
PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; American Home Products Corporation
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008203	A2	20020131	WO 2001-US23097	20010720
WO 2002008203	A3	20020523		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002052375	A1	20020502	US 2001-910466	20010719

PRIORITY APPLN. INFO.: US 2000-220131P P 20000721
OTHER SOURCE(S): MARPAT 136:135018
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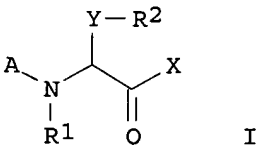


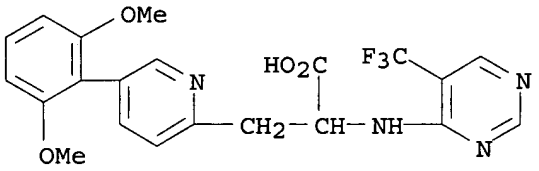
I

AB 3-(Heteroaryl)alanine derivs. I [A = an (un)substituted aryl, heteroaryl,

cycloalkyl, or heterocyclic group; R2 = a nitrogen contg. (un)substituted, heteroaryl; Y = (CH2)m; m = 0 or 1; R1 = H, (un)substituted, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, or heterocyclic; X = OH, (un)substituted alkoxy, alkenoxy, cycloalkoxy, cycloalkenoxy, aryloxy, heteroaryloxy, heterocyclyloxy, or NR3R3 [R3 = H, (un)substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclic]] were prepd. as inhibitors of **leukocyte** adhesion mediated by VLA-4. Compds. I have binding affinity to VLA-4 as expressed by an IC50 of about 15 .mu.M or less. Thus, N-[5-(2,2,2-trifluoroethyl)pyrimidin-4-yl]-DL-3-[5-(2,5-dimethoxyphenyl)pyridin-2-yl]alanine was prepd. by multistep procedure via coupling of DL-[5-(2,6-dimethoxyphenyl)pyridine-2-yl]alanine Et ester and 4,6-dichloro-5-(2,2,2-trifluoroethyl)pyrimidine.

IT **392298-39-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of alanine derivs. as inhibitors of **leukocyte** adhesion mediated by VLA-4)

RN 392298-39-4 CAPLUS
CN 2-Pyridinepropanoic acid, 5-(2,6-dimethoxyphenyl)-.alpha.-[[5-(trifluoromethyl)-4-pyrimidinyl]amino]- (9CI) (CA INDEX NAME)



L7 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:90022 CAPLUS
DOCUMENT NUMBER: 136:129056
TITLE: .alpha.-Amino acid derivatives for inhibitors of **leukocyte** adhesion mediated by VLA-4
INVENTOR(S): Konradi, Andrei W.; Pleiss, Michael A.; Thorsett, Eugene D.; Ashwell, Susan; Welmaker, Gregory S.; Kreft, Anthony; Sarantakis, Dimitrios; Dressen, Darren B.; Grant, Francine S.; Semko, Christopher; Xu, Ying-Zi
PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; American Home Products Corporation
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008202	A2	20020131	WO 2001-US23075	20010720

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

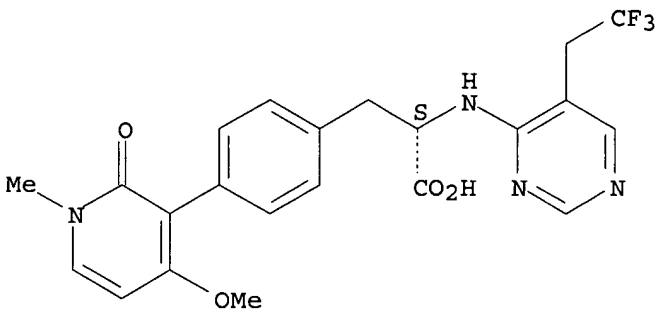
US 2002052470 A1 20020502 US 2001-910702 20010720
PRIORITY APPLN. INFO.: US 2000-220132P P 20000721
OTHER SOURCE(S): MARPAT 136:129056

AB Disclosed are certain .alpha.-amino acid compds. which bind VLA-4. Certain of these compds. also inhibit **leukocyte** adhesion and, in particular, **leukocyte** adhesion mediated by VLA-4. Such compds. are useful in the treatment of inflammatory diseases in a mammalian patient, e.g., human, such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compds. can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis. Prepn. of N-[5-(2,2,2-trifluoroethyl)pyrimidin-4-yl]-L-4'-(1-methyl-4-methoxy-2-pyridon-3-yl)phenylalanine is described.

IT **393138-31-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(.alpha.-amino acid derivs. for inhibitors of **leukocyte** adhesion mediated by VLA-4, and therapeutic use)

RN 393138-31-3 CAPLUS
CN L-Phenylalanine, 4-(1,2-dihydro-4-methoxy-1-methyl-2-oxo-3-pyridinyl)-N-[5-(2,2,2-trifluoroethyl)-4-pyrimidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

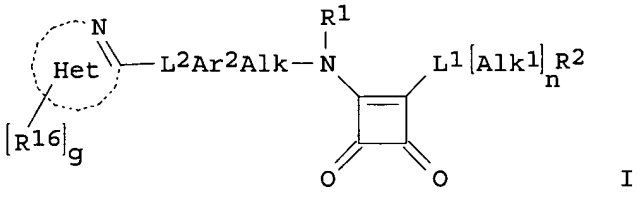


L7 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:51439 CAPLUS
DOCUMENT NUMBER: 136:118460
TITLE: Preparation of squaric acid derivatives containing a bicyclic heteroaromatic ring as integrin antagonists
INVENTOR(S): Langham, Barry John; Alexander, Rikki Peter; Head, John Clifford; Linsley, Janeen Marsha; Porter, John Robert; Archibald, Sarah Catherine; Warrellow, Graham John
PATENT ASSIGNEE(S): Celltech R & D Limited, UK
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

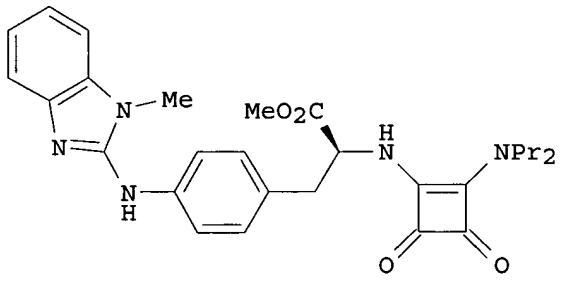
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004426	A1	20020117	WO 2001-GB3028	20010705

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 2002107263 A1 20020808 US 2001-899488 20010705
PRIORITY APPLN. INFO.: GB 2000-16785 A 20000707
GB 2000-28364 A 20001121
OTHER SOURCE(S): MARPAT 136:118460
GI



I



II

AB The title compds. [I; Het = (un)substituted bicyclic fused ring heteroarom. group; R16 = H, alkyl, etc.; g = 0-4; L2 = a bond, O, S, CO, etc.; Ar2 = (un)substituted (hetero)arom.; Alk = CH2CHR, CH:CR, CH(CH2R), C(:CHR) (wherein R = CO2H or a deriv. or biostere thereof); R1 = H, alkyl; L1 = a covalent bond, a linker atom or group; Alk1 = (un)substituted aliph. chain; n = 0-1; R2 = H, (un)substituted heteroaliph., cycloaliph., heterocycloaliph., polycycloalphatic, heteropolycycloaliph., arom. or heteroarom. group other than a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl] which are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders, or disorders involving the inappropriate growth or migration of cells, were prepd. Thus, reacting Et (S)-2-amino-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate.CF3CO2H with diisopropylsquarate in the presence of DIPEA in iso-Pr followed by treatment of the resulting Et (S)-2-{[2-(isopropoxy)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoate with dipropylamine in MeOH afforded II. The exemplified compds. I showed IC50 of .ltoreq. 1 .mu.M in the .alpha.4.beta.1 and .alpha.4.beta.7 assays.

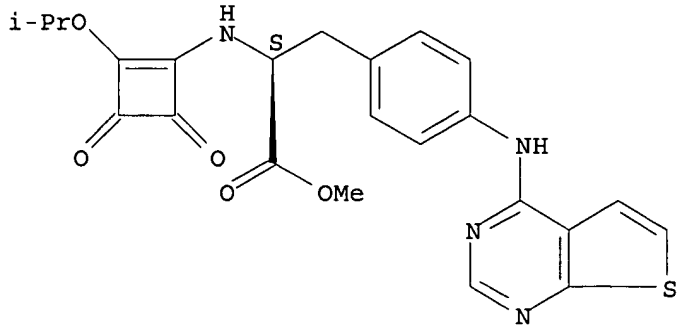
IT **389637-06-3P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of squaric acid derivs. contg. a bicyclic heteroarom. ring as integrin antagonists)

RN 389637-06-3 CAPLUS

CN L-Phenylalanine, N-[2-(1-methylethoxy)-3,4-dioxo-1-cyclobuten-1-yl]-4-

(thieno[2,3-d]pyrimidin-4-ylamino)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:868260 CAPLUS
DOCUMENT NUMBER: 136:627
TITLE: Combinations of enzyme inhibitor-containing preparations and the use in inhibition of mononuclear cells and T-cells and treatment of immune conditions
INVENTOR(S): Ansorge, Siegfried; Arndt, Marco; Buehling, Frank; Lendeckel, Uwe; Neubert, Klaus; Reinhold, Dirk
PATENT ASSIGNEE(S): Institut fuer Medizintechnologie Magdeburg G.m.b.H. IMTM, Germany
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001089569	A1	20011129	WO 2001-EP5887	20010522
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10025464	A1	20011206	DE 2000-10025464	20000523

PRIORITY APPLN. INFO.: DE 2000-10025464 A 20000523

AB A method is disclosed which permits, owing to the simultaneous and joint inhibition of the enzyme activities of (1) alanyl-aminopeptidase and dipeptidyl-peptidase IV, (2) dipeptidyl-peptidase IV and angiotensin-converting enzyme, (3) dipeptidyl-peptidase IV and prolyl-oligopeptidase, and (4) dipeptidyl-peptidase IV and X-Pro-aminopeptidase, the inhibition of DNA synthesis and thus the proliferation of mononuclear cells and T cells to an extent which cannot be obtained by individual application of the enzyme inhibitors, even when used in higher doses. Although the above-mentioned inhibitors influence the same process, namely DNA synthesis and thus the proliferation of immune cells, this effect is not complete and not long-lasting when the

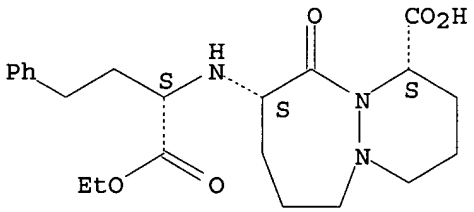
inhibitors are used individually. The functional overlapping of enzymic activities results, as is supported by exptl. data, in an additive/superadditive inhibitory effect on DNA synthesis and the proliferation resulting from the simultaneous inhibition of a plurality of the above enzymes. The invention shows that the simultaneous application of inhibitors of the above enzymes or of corresponding prepns. and forms of administration is suitable for the therapy of autoimmune diseases and chronic diseases with an inflammatory genesis, as well as for the treatment of post-transplant rejection episodes.

IT **88768-40-5**, Cilazapril
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme inhibitor combinations for inhibition of mononuclear cells and T-cells and treatment of immune conditions)

RN 88768-40-5 CAPLUS

CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:513679 CAPLUS
DOCUMENT NUMBER: 133:120681
TITLE: Preparation of amino acid acyl derivatives as inhibitors of **leukocyte** adhesion mediated by VLA-4
INVENTOR(S): Konradi, Andrei; Pleiss, Michael A.; Thorsett, Eugene D.; Ashwell, Susan; Welmaker, Gregory S.; Kreft, Anthony; Sarantakis, Dimitrios; Dressen, Darren B.; Grant, Francine S.; Semko, Christopher; Xu, Ying-Zi
PATENT ASSIGNEE(S): Elan Pharmaceuticals, Inc., USA; American Home Products
SOURCE: PCT Int. Appl., 342 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043372	A1	20000727	WO 2000-US1686	20000121

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1144388	A1	20011017	EP 2000-913245	20000121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000007663	A	20020507	BR 2000-7663	20000121
NO 2001003600	A	20010920	NO 2001-3600	20010720

PRIORITY APPLN. INFO.:	US 1999-116923P	A2	19990122
	US 1999-160999P	P	19991021
	WO 2000-US1686	W	20000121

OTHER SOURCE(S): MARPAT 133:120681

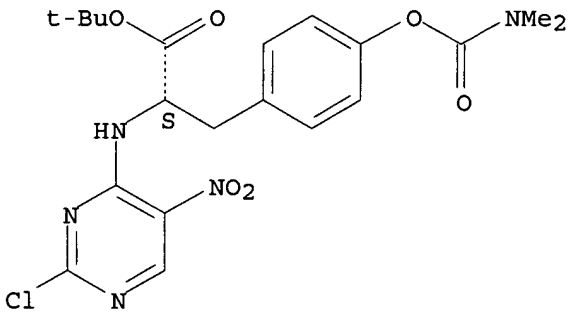
AB Disclosed are compds. R2-W:CR1-Q-CR3R3'COX and R2-W'-CHR1-Q-CR3R3'COX [R1 and R2 are joined to form a ring; R3, R3' = H, iso-Pr, -CH2Z or :CHZ, where Z = H, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxy, carboxyalkyl, etc.; Q = O, S, SO, SO2, NH or imino group; W = nitrogen, carbon; W' = nitrogen, carbon, oxygen, sulfur, SO, SO2; X = OH, (un)substituted alkoxy, alkenoxy, cycloalkoxy, cycloalkenoxy, aryloxy, heteroaryloxy or heterocyclyloxy, an amino group] which bind VLA-4. Thus, N-[5-(N-4-toluenesulfonylamino)pyrimidin-4-yl]-L-4-(N,N-dimethylcarbamyloxy)phenylalanine tert-Bu ester was prepd. by condensation of L-4-(N,N-dimethylcarbamyloxy)phenylalanine tert-Bu ester with 2,4-dichloro-5-nitropyrimidine, followed by nitro group redn. and tosylation. Compds. synthesized in the examples are expected to have a binding affinity to VLA-4 expressed by an IC50 of 15 .mu.M or less.

IT **285139-31-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of amino acid acyl derivs. as inhibitors of **leukocyte** adhesion mediated by VLA-4)

RN 285139-31-3 CAPLUS

CN L-Tyrosine, N-(2-chloro-5-nitro-4-pyrimidinyl)-, 1,1-dimethylethyl ester, dimethylcarbamate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	2000:513676 CAPLUS
DOCUMENT NUMBER:	133:120679
TITLE:	Preparation of heterocyclyl amino acid derivatives as inhibitors of **leukocyte** adhesion mediated by VLA-4
INVENTOR(S):	Konradi, Andrei W.; Pleiss, Michael A.; Thorsett, Eugene D.; Ashwell, Susan; Sarantakis, Dimitrios; Welmaker, Gregory S.; Kreft, Anthony; Semko, Christopher; Sullivan, Robert Warren; Soares, Christopher Joseph; Ly, Kiev Sui; Tarby, Christine M.
PATENT ASSIGNEE(S):	Elan Pharmaceuticals, Inc., USA; American Home

Products Corporation
SOURCE: PCT Int. Appl., 305 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043369	A1	20000727	WO 2000-US1540	20000121
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1144384	A1	20011017	EP 2000-904487	20000121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-116923P A2 19990122
US 1999-160999P P 19991021
WO 2000-US1540 W 20000121

OTHER SOURCE(S): MARPAT 133:120679

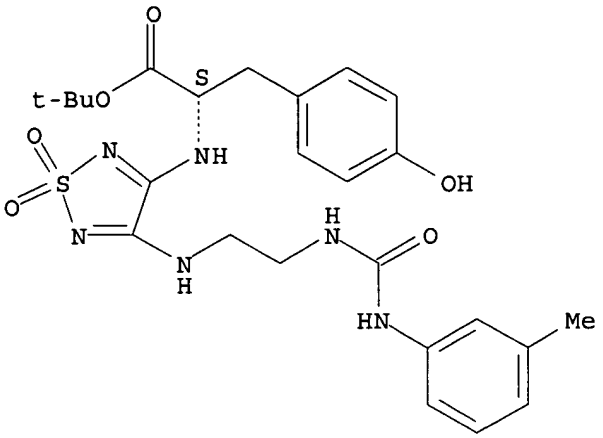
AB Disclosed are compds. R2-W:CR1-Q-CR3R3'COX and R2-W'-CHR1-Q-CR3R3'COX [R1 and R2 are joined to form a ring; R3, R3' = H, iso-Pr, -CH2Z or :CHZ, where Z = H, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxy, carboxyalkyl, etc.; Q = O, S, SO, SO2, NH or imino group; W = nitrogen, carbon; W' = nitrogen, carbon, oxygen, sulfur, SO, SO2; X = OH, (un)substituted alkoxy, alkenoxy, cycloalkoxy, cycloalkenoxy, aryloxy, heteroaryloxy or heterocyclyloxy, an amino group] which bind VLA-4. Thus, N-[6-[N-benzyl-N-(1-phenylethyl)amino]-4-chloro-1,3,5-triazin-2-yl]-L-4-(dimethylcarbamyloxy)phenylalanine was prepd. by condensation of cyanuric chloride with tyrosine O-(dimethylcarbamate) tert-Bu ester and N-benzylphenethylamine, followed by sapon. Compds. synthesized in the examples are expected to have an IC50 of 15 .mu.M or less.

IT **285140-16-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of heterocyclyl amino acid derivs. as inhibitors of **leukocyte** adhesion mediated by VLA-4)

RN 285140-16-1 CAPLUS

CN L-Tyrosine, N-[4-[[2-[[[(3-methylphenyl)amino]carbonyl]amino]ethyl]amino]-1,1-dioxido-1,2,5-thiadiazol-3-yl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:69479 CAPLUS
DOCUMENT NUMBER: 128:200763
TITLE: ACE-inhibition prevents postischemic coronary **leukocyte** adhesion and **leukocyte** -dependent reperfusion injury
AUTHOR(S): Kupatt, Christian; Habazettl, Helmut; Zahler, Stefan; Weber, Christian; Becker, Bernhard F.; Messmer, Konrad; Gerlach, Eckehart
CORPORATE SOURCE: Dep. Physiol., Ludwig-Maximilians-Univ., Munich, 80336, Germany
SOURCE: Cardiovascular Research (1997), 36(3), 386-395
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Polymorphonuclear **leukocytes** (PMN), retained in the microvascular bed, can contribute to postischemic myocardial reperfusion injury. Since a beneficial effect of ACE-inhibition on reperfusion injury has been reported, the authors investigated the impact of cilazaprilat on PMN dependent reperfusion injury in isolated guinea pig hearts. Hearts (per group) were subjected to 15 min of ischemia. Immediately thereafter, a bolus of PMN was injected into the coronary system. External heart work (EHW) and total cardiac nitric oxide release were measured. For microscopic evaluation, hearts received rhodamine 6G labeled PMN after ischemia, were arrested 5 min later, and further perfused with FITC dextran (0.1%). Localization of retained PMN was assessed by fluorescence microscopy. **Leukocyte** activation was studied by FACS anal. of the adhesion mol. CD11b before and after coronary passage of the PMN. The ACE-inhibitor cilazaprilat (Cila, 2 .mu.M) and the NO-synthase inhibitor nitro-L-arginine (NOLAG, 10 .mu.M) were used to modulate nitric oxide formation of the heart. Postischemic EHW recovered to 67% (controls) and 64% (Cila) of the preischemic value. Addn. of PMN severely depressed recovery of EHW (39%) and NO release (39% of the preischemic value). Simultaneously, ischemia led to a substantial increase in postcapillary PMN adhesion (from 21 to 172 PMN/mm2 surface) and CD11b-expression of the recovered PMN (3-fold). Cila attenuated postischemic PMN adhesion (83 PMN/mm2) and activation of PMN, whereas it improved recovery of work performance (64%) and NO release (65%) in the presence of PMN. Conversely, NOLAG increased PMN adhesion (284 PMN/mm2) and myocardial injury. Thus, ACE-inhibition prevents **leukocyte** dependent

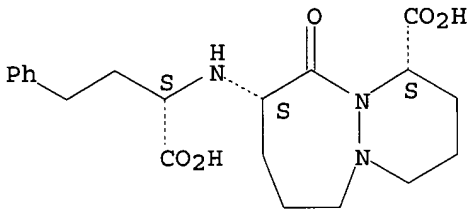
reperfusion injury mainly by inhibition of postcapillary **leukocyte** adhesion. The effect may be mediated by NO, given the proadhesive effect of NOLAG.

IT **90139-06-3**, Cilazaprilat
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACE-inhibition prevents **leukocyte**-dependent reperfusion injury via inhibition of postcapillary **leukocyte** adhesion)

RN 90139-06-3 CAPLUS

CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-carboxy-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:805307 CAPLUS

DOCUMENT NUMBER: 128:136326

TITLE: Effects of ACE-inhibition on redox status and expression of P-selectin of endothelial cells subjected to oxidative stress

AUTHOR(S): Zahler, S.; Kupatt, C.; Mobert, J.; Becker, B. F.; Gerlach, E.

CORPORATE SOURCE: Department of Physiology, University of Munich, Munich, 80336, Germany

SOURCE: Journal of Molecular and Cellular Cardiology (1997), 29(11), 2953-2960
CODEN: JMCDAY; ISSN: 0022-2828

PUBLISHER: Academic Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Redox stress during post-ischemic reperfusion may be the prime signal for processes leading to myocardial remodelling and hypertrophy. Nitric oxide (NO) is antioxidative, antiadhesive for neutrophils (PMN) and antiproliferative. Thus, enhancing endothelial prodn. of NO, e.g. by inhibiting breakdown of endogenous bradykinin via angiotensin converting enzyme (ACE), could be beneficial. The effect of cilazaprilat (CILA, 10 .mu.M), an ACE inhibitor, on redox status, expression of the adhesion mol. P-selectin, and PMN adhesion under conditions of oxidative stress was investigated in cultured human umbilical vein endothelial cells (HUVECs). Incubation of the cells with H2O2 (0.1 and 1 mM) for 15 min served as oxidative stimulus. The intra- and extracellular concns. of reduced and oxidized glutathione (GSH and GSSG) were measured by HPLC as indicators of endothelial redox status. Expression of P-selectin was measured by flow cytometry. Furthermore, firm **leukocyte** adhesion to HUVECs was assessed. In controls, the intracellular ratio GSH/GSSG averaged 47 and dropped to 30 after incubation with 0.1 mM H2O2. The ratio declined to 6.5 with 1 mM H2O2, CILA blocked the effects of 0.1 mM H2O2, but was ineffective against 1 mM peroxide. The extracellular ratio did not discriminate between 0.1 and 1 mM H2O2, falling from 18 to 1 in both situations. P-selectin expression rose from 100% (control) to 146% after 1 mM H2O2 without CILA, but only to 114% in the presence of CILA. PMN

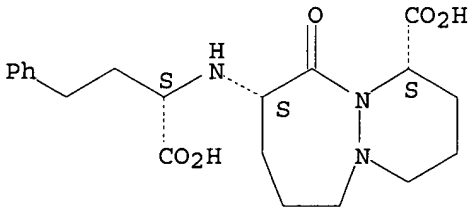
adhesion was enhanced from about 1600 PMN per microwell (control) to 4300/well by 1 mM H2O2. CILA had no significant effect on adhesion (3900 PMN/well). Exposure of HUVECs to 0.1 mM H2O2 affected neither P-selectin expression nor PMN adhesion. Consequently, ACE inhibition can mitigate mild (0.1 mM H2O2) but not more severe redox stress in HUVECs. Irresp., CILA reduced the upregulation of P-selectin at the higher H2O2 concn., indicating that this process is regulated independently of the cellular redox status. The firm adhesion of PMN to HUVECs was independent of P-selectin expression.

IT **90139-06-3**, Cilazaprilat
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of ACE-inhibition on redox status and expression of P-selectin of endothelial cells subjected to oxidative stress)

RN 90139-06-3 CAPLUS

CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-carboxy-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:360040 CAPLUS

DOCUMENT NUMBER: 127:44670

TITLE: Granulocyte activation by passage through a reperfused coronary bed: functional consequences of ACE inhibition

AUTHOR(S): Zahler, S.; Kupatt, C.; Becker, B.F.; Gerlach, E.

CORPORATE SOURCE: Department of Physiology, University of Munich, Germany

SOURCE: World Congress for Microcirculation, 6th, Munich, Aug. 25-30, 1996 (1996), 461-464. Editor(s): Messmer, Konrad; Kuebler, Wolfgang M. Monduzzi Editore: Bologna, Italy.
CODEN: 64KQAW

DOCUMENT TYPE: Conference

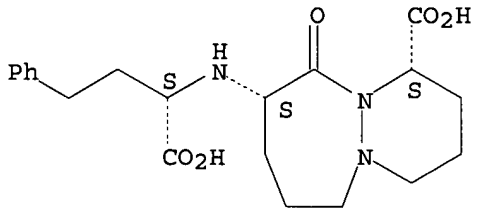
LANGUAGE: English

AB External heart work (EHW), NO release, intracoronary PMN retention, and CD11b expression on PMN were detd. in reperfused isolated hearts, without and with modulation of NO metab. by Cilazaprilat (CIL), an ACE inhibitor. EHW recovered postischemic to 67% and 33% in hearts without and with PMN, resp. After ACE inhibition with CIL, it recovered to 65%. Postischemic NO amounted to 59% of the preischemic value, but to only 32% in the presence of PMN, vs. 64% with PMN and CIL. PMN retention in non-ischemic hearts was 23% of the applied no., and 38% after 15min ischemia. CIL reduced postischemic PMN retention to 25%. CD11b expression on PMN was unaltered by passage through nonischemic coronaries, while ischemia increased it 3-fold; CIL blocked this effect. Thus, ACE inhibition preserves NO and cardiac function during reperfusion, and reduces PMN adhesion and activation.

IT **90139-06-3**, Cilazaprilat
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(granulocyte activation by passage through reperfused coronary bed: functional consequences of ACE inhibition)
RN 90139-06-3 CAPLUS
CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-carboxy-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

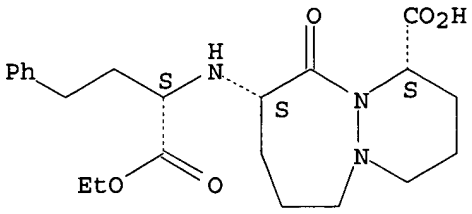
Absolute stereochemistry.



L7 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:191352 CAPLUS
DOCUMENT NUMBER: 126:272066
TITLE: Angiotensin converting enzyme inhibitors suppress production of tumor necrosis factor-.alpha. in vitro and in vivo
AUTHOR(S): Fukuzawa, Masamitsu; Satoh, Jo; Sagara, Mikio; Muto, Gen; Muto, Yoshiko; Nishimura, Sachiko; Miyaguchi, Shuichi; Qiang, Xiao Ling; Sakata, Yoshiyuki; Nakazawa, Tetsuya; Ikehata, Fumiko; Ohta, Setsu; Toyota, Takayoshi
CORPORATE SOURCE: Third Department of Internal Medicine, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, 980-77, Japan
SOURCE: Immunopharmacology (1997), 36(1), 49-55
CODEN: IMMUDP; ISSN: 0162-3109
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has been reported that angiotensin converting enzyme (ACE) inhibitors have beneficial effects on insulin resistance and congestive heart failure, in which elevations of serum tumor necrosis factor-.alpha. (TNF-.alpha.) level have been indicated. Therefore, in this study, we examd. effect of ACE inhibitors on TNF-.alpha. prodn. both in vitro and in vivo by using human blood mononuclear cells and mice, resp. LPS (20 .mu.g/mL)-induced in vitro TNF-.alpha. prodn., measured by bioassay and ELISA, was significantly inhibited with captopril, delapril and cilazapril in a concn. of 10-3 mol/l. A single, oral administration of captopril, delapril and cilazapril at more than 10-fold doses of common clin. use in man significantly inhibited LPS (2 mg/kg)-induced serum TNF-.alpha. activity in Balb/c mice. These results indicate that ACE inhibitors such as captopril, delapril and cilazapril have an inhibitory effect on TNF-.alpha. prodn. not only in vitro as previously reported, but also in vivo, although relatively high concns. and large doses were required in this study.
IT **88768-40-5**, Cilazapril
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin converting enzyme inhibitors suppress tumor necrosis factor-.alpha. formation)
RN 88768-40-5 CAPLUS
CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-

(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:845231 CAPLUS
DOCUMENT NUMBER: 123:275949
TITLE: Angiotensin-converting-enzyme inhibitors suppress synthesis of tumor necrosis factor and interleukin 1 by human peripheral blood mononuclear cells
AUTHOR(S): Schindler, Ralf; Dinarello, Charles A.; Koch, Karl-M.
CORPORATE SOURCE: Department of Nephrology, Medical School Hannover, Berlin, D-14050, Germany
SOURCE: Cytokine (1995), 7(6), 526-33
CODEN: CYTIE9; ISSN: 1043-4666
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

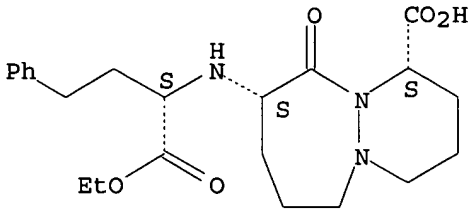
AB Administration of angiotensin-converting-enzyme (ACE) inhibitors reduce vascular proliferation following endothelial injury as well as progression of renal disease in various animal models. These effects might be due to interference with cytokines such as interleukin 1 (IL-1) or tumor necrosis factor .alpha. (TNF) since they have been implicated in regulating the effects of vascular cell growth factors such as fibroblast- and platelet-derived growth factors. The authors investigated the in vitro synthesis of IL-1 and TNF from human peripheral blood mononuclear cells (PBMC) in the presence of various ACE-inhibitors. Captopril dose-dependently suppressed the IL-1.beta. induced synthesis of TNF by 74% and the IL-1.beta.-induced synthesis of IL-1.alpha. by 60%. Cytokine synthesis induced by lipopolysaccharide was less affected. At concns. suppressing TNF and IL-1, captopril did not reduce the synthesis of complement C3 in the same cells. Enalapril and cilazapril also suppressed cytokine-induced cytokine synthesis. Ramipril, lisinopril, perindopril and spirapril had no significant effect on TNF synthesis suggesting that the effect was not related specifically to the inhibition of ACE. Accumulation of mRNA for IL-1 and TNF were not affected by captopril, suggesting a posttranscriptional effect. The authors conclude that certain ACE-inhibitors suppress IL-1 and TNF synthesis at a posttranscriptional level and might therefore influence cytokine-mediated cell growth.

IT **88768-40-5**, Cilazapril
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ACE inhibitors suppress synthesis of tumor necrosis factor and interleukin 1 by human peripheral blood mononuclear cells)

RN 88768-40-5 CAPLUS
CN 6H-Pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, 9-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-, (1S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

09/ 910,702



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L3 3 S L1
L4 838 S L1 FUL
L5 619 S L1 SUB=L2 FULL

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L6 500 S L5
L7 14 S L6 AND LEUKOCYTE?

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